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Maureen Obianuju Okafor Date

Geographic Disparities in Survival of Early-Stage Colorectal Adenocarcinoma for Patients Undergoing Colon Resection: a U.S. Population-Based Study

By

Maureen Obianuju Okafor
Master of Public Health

Global Epidemiology

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Kevin C. Ward, PhD, MPH, CTR
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Abstract

Geographic Disparities in Survival of Early-Stage Colorectal Adenocarcinoma for Patients Undergoing Colon Resection: a U.S. Population-Based Study
By Maureen Obianuju Okafor

Introduction: Colorectal cancer is the third most commonly diagnosed cancer and the second leading cause of cancer death among both men and women worldwide. Based on scientific evidence, limited access to care for patients living in remote rural areas or in small urban areas far from healthcare services is associated with poorer health outcomes. In order to better understand the importance of geographic differences and CRC patient care in the United States, this study seeks to investigate the geographic disparity in the survival of early-stage colorectal adenocarcinoma following surgery.

Materials and methods: A U.S. population-based retrospective cohort study using data from the Surveillance, Epidemiology, and End Results (SEER) Program was conducted. We identified 54,482 eligible cases of colorectal adenocarcinoma diagnosed between 2007 and 2011 from the 18 SEER cancer registries. To assess the differences in survival of colorectal adenocarcinoma by geographic location and the U.S. Census regions, Kaplan-Meier survival curves and multivariate Cox proportional hazard models were constructed. We presented the results of our multivariate analysis as adjusted hazard ratios (HR) with corresponding 95% confidence intervals.

Results: Kaplan-Meier survival curves and 5-year relative survival estimates indicated significantly better outcomes in metro counties (92%) compared to non-metro adjacent (87.3%) and non-metro non-adjacent areas (89.6%). Although insignificant, we found it surprising that the adjusted hazard ratio for non-metro non-adjacent areas compared to metro areas was higher than that for non-metro adjacent areas. A statistically non-significant 10% increase in the risk of death from colorectal adenocarcinoma was observed among cases in non-metro adjacent areas compared to those in metro counties (HR: 1.10, 95% CI: 0.97, 1.24). No substantial difference in cancer-specific mortality risk was found between metro and non-metro non-adjacent areas (HR: 1.04, 95% CI: 0.90, 1.20). Age at diagnosis, marital status and cancer stage were found to be strong predictors of survival in the United States.

Conclusion: There is a growing need for further research studies which will take into account geographic characteristics that aid in assessing access to and use of healthcare services among cancer patients, and ultimately, provides value towards improved health outcomes.

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LITERATURE REVIEW

Colorectal cancer

Colorectal cancer (CRC), a leading cause of morbidity and mortality worldwide, is a malignant disease in which cancer cells form in the mucosal lining of the colon (large intestine) or rectum with the potential to invade its wall and spread to other organs of the body. It is the third most commonly diagnosed cancer and the second leading cause of cancer death among both men and women worldwide (1-4). About 98% of colon and rectal cancers are adenocarcinomas, a histologic subtype, of which approximately 80% arise from pre-existing adenomatous polyps. Less frequently occurring subtypes include carcinoid, lymphoma, sarcoma and squamous cell types. Approximately 65% of all colorectal cancers develop in the sigmoid, cecum, rectum and rectosigmoid junction (1, 5).

Epidemiology

Colorectal cancer is a worldwide concern, comprising about 9.7% of the global cancer burden, with an annual incidence of approximately 1.3 million cases and a mortality of 700,000 cases (6, 7). This burden is anticipated to increase by 60% to over 2.2 million new cases and 1.1 million cancer deaths by 2030 (8). Although approximately 55% of cases occur in more developed regions such as Australia/New Zealand, Europe, North America and Eastern Asia, mortality is lower (8.5% of total) compared to mortality rates of over 52% in less developed and economically transitioning regions such as Central and Eastern Europe (7, 9). In 2013, Ferlay and colleagues reported that Europe faced a 13% burden of colorectal cancer, probably due to some of its countries' still budding cancer screening programs (10, 11). A retrospective study conducted in Tanzania by Chalya et al found that regardless of the lack of information on colorectal cancer, the incidence and mortality were significant (4.7% and 10.5% respectively) as a result of an increasing “westernized” lifestyle. Most patients presented late at a relatively young age with advanced disease (12).

In the United States, despite a measurable decline in incidence and mortality over the past two decades, colorectal cancer remains the third most common cancer among men and women combined. The American Cancer Society estimates that 95,270 new cases of colon cancer and 39,220 new cases of rectal cancer will be diagnosed in 2016; 70,820 new cases of colorectal cancer are expected in men and 63,670 in women. The United States, one of few countries that have shown a downward trend in incidence rates, has largely attributed this progress to improved risk factor profiles, lifestyle modification and an increase in colorectal cancer screening among adults 50 years of age and older. This trend, however, has been noted to differ by age, declining by 4.5% per year among adults 50 years and older, but increasing by 1.8% per year among those younger than 50 years (4, 13). Reasons for this difference remain unclear. It is expected that 49,190 deaths from colorectal cancer will occur in the United States in 2016. A decrease in the number of deaths per 100,000 population per year, due in part to enhanced early detection and treatment of colorectal cancer, has increased the 5-year overall survival to about 65%, with variation across socioeconomic status, race and ethnic subgroups (13-15). Survival of colorectal cancer is also highly dependent on the stage of disease at diagnosis; localized (stage I), regional (stage IIA to IIIC) and distant (stage IV) stage CRC have 5-year relative survival rates of 90%, 70% and 10% respectively (13, 16, 17). Overall, the lifetime risk of colorectal cancer is about 1 in 21 (4.7%) for men and 1 in 23 (4.4%) for women (4). Difference in CRC susceptibility between sexes is not well understood; however, hormonal and environmental factors may be involved.

Risk factors

Etiologic factors implicated in colorectal carcinogenesis include inflammatory bowel disease, inherited genetic syndromes such as Lynch syndrome (formerly hereditary non-polyposis colorectal cancer, or HNPCC) and familial adenomatous polyps (FAP), and acquired gene mutations occurring in the *APC*, *KRAS*, *p53* and *SMAD4* genes which disrupt cell growth regulation. Other etiologic factors include age, race, family history of colorectal cancer, dietary exposure to red meat, animal fat and low-fiber foods, excessive alcohol consumption, smoking, diabetes and obesity. Although diet has been shown to increase the risk of colorectal cancer, it is still unclear if there exists any influence on a person with an established disease (13, 17-20).

Prevention

Many previous studies have linked high-fiber intake, vegetables and fruits, non-steroidal anti-inflammatory drugs (NSAIDs), hormone replacement therapy, increased physical activity, and reduction of smoking and alcohol ingestion to a reduced risk of colorectal cancer. In given populations, these associations with colorectal cancer may appear inconsistent. However, as subsets of the population with susceptibility to specific factors are uncovered, preventive measures can be better fashioned (13, 21-23). Because colorectal cancer develops slowly and typically does not present with symptoms until late stage, early detection using screening tests is key to the prevention of this disease and the limitation of complications following advanced stage disease. The screening process aims to detect cancer or pre-cancerous polyps in persons who have no observable symptoms of the disease. These tests include guaiac-based fecal occult blood test (gFOBT), fecal immunochemical test (FIT), stool DNA test, flexible sigmoidoscopy, full colonoscopy, double-contrast barium enema and when possible, a CT colonography (virtual colonoscopy) (24). Each screening method possesses its own advantage relative to other methods. However, geographic variations in these screening procedures exists (25-28). Evidence suggests that rural residents are less likely than urban residents to receive CRC screening (multivariate odds ratio, 0.65; 95% CI: 0.53-0.79) (3). As has been found with breast cancer screening programmes, this difference may be associated with distance from cancer screening sites and area-level poverty rate (29, 30). Based on data from previous studies, the American Cancer Society recommends colorectal cancer screening comprising an annual gFOBT, a sigmoidoscopy every 5 years or a colonoscopy every 10 years starting at 50 years of age for individuals of average risk and earlier for high-risk individuals (2, 4, 17, 30, 31).

Diagnosis and treatment modalities

Colorectal cancer is known to have an insidious onset and presents asymptomatically in its early stages. As the disease progresses, symptoms develop as a result of growth of the tumor into the bowel lumen and/or through the organ wall. Symptoms may include changes in bowel habit or stool caliber, blood in the stool, rectal bleeding, a feeling of incomplete bowel emptying, abdominal pain or cramps, weakness, fatigue and unintended weight loss (13, 32). A diagnosis is confirmed histologically on pathologic examination of tumor tissue and pathologic staging takes place after surgical exploration of the abdomen and cancer-directed surgical resection. The most commonly used CRC staging system is the American

Joint Committee on Cancer (AJCC) TNM classification (33). CRC staging determines the extent of the cancer in the body and is one of the most important factors in determining the appropriate treatment approach (2, 17). Treatment options in the management of colorectal cancer include surgery, chemotherapy and radiation therapy. Surgical resection is the primary treatment for localized resectable colon cancer; chemotherapy alone or in combination with radiation therapy is offered as neoadjuvant or adjuvant therapy for regional cancers (4, 13, 24). In the event of metastatic spread, treatment typically includes chemotherapy with or without targeted therapy (4). A recent study by Wancata et al using SEER data found that compared to patients with advanced CRC who did not undergo surgery, those who underwent cancer-directed surgery had better survival estimates (HR: 2.22, 95% CI: 2.17, 2.27) (34). The goals of care following CRC treatment encompass surveillance for recurrence, management of early and late complications associated with treatment, encouragement of healthy lifestyle choices and adherence to recommended preventive guidelines (35).

Geographic differences in colorectal cancer survival

In general, prognostic factors for CRC survival include tumor stage, grade, histologic type, age at diagnosis, sex, socioeconomic status, race, ethnicity and treatment type. In a population-based study using New Jersey statewide cancer registry, Henry et al found that adjustments for age, stage and socioeconomic deprivation changed the geographic survival patterns of colorectal cancer indicating that these adjustment factors may be contributory to CRC survival disparities (36). Factors identified by Georgescu and colleagues to negatively impact overall colorectal adenocarcinoma survival were advanced age at diagnosis, advanced AJCC/UICC stage, moderate to low CRC grade, emergency surgery related to cancer complications, disease recurrence and insufficient chemotherapy (37). Other known prognostic factors include primary tumor site and lymphovascular invasion (38). Access to diagnostic and treatment services has also been implicated (16). A population-based study conducted in Manitoba to assess geographic differences in quality of treatment and cancer outcome found inconclusive differences in quality measures and by implication, in CRC survival (39). In contrast, Beckmann et al studied 4,641 cases in South Australia and found that patients with potentially curable CRC living in remote areas had significantly worse outcomes than those living in metropolitan areas (40).

Although several international and US study findings have shown geographic variation in CRC screening and treatment (3, 25, 27, 28, 41-43), fewer studies have sought to find geographic variations in CRC survival using US population-based cancer registries. Furthermore, very little is known of the variation in CRC survival following colorectal resection; none to our knowledge has done this using US population-based cancer registry data. Based on a study conducted in the Wessex region of southern England, CRC patients living further from a treatment center (more than 30 km) showed worse prognosis following surgery, especially within 30 days of the procedure. While reasons for this disparity did not seem to include socioeconomic factors, a highly significant relationship between district of treatment and survival following surgery was found to exist (44).

Rural-urban classifications and access to colorectal cancer care

Historically, many research studies conducted to identify geographic disparities utilize rural-urban classifications dependent upon a definition of ‘rural’ and ‘urban’. Creating a clear distinction between rural and urban areas has proven difficult because of the multidimensional nature of these geographic locations. As such, multiple definitions and classifications exist based on administrative need, land-use or socioeconomic influences and researchers and policymakers take on the task to determine appropriate measures for each endeavor (45). Although the choice of rural definition used in research should be based on the purpose of the study, availability of data is a major determining factor. For lack of ideal classifications, many research studies in healthcare utilize rural-urban definitions which are based on features such as population density, geographic isolation, population size and socioeconomic deprivation (46, 47). These definitions, albeit indicative of population, education, poverty level and socioeconomic status, may not sufficiently predict access to patient care.

The 2013 Rural-Urban Continuum Codes, developed by the United States Department of Agriculture (USDA), form a classification scheme that distinguishes metropolitan (metro) counties by the population size of their metro areas, and non-metropolitan (non-metro) counties by degree of urbanization and adjacency to a metro area (Figure 1) (48). The Rural-Urban Continuum Codes (RUCC) classifies all counties in the United States into 9 categories: 1) counties in metro areas of 1 million population or more, 2) counties in metro areas of 250,000 to 1 million population, 3) counties in metro areas of fewer than 250,000 population, 4) urban population of 20,000 or more, adjacent to a metro area, 5) urban population of 20,000 or more, not adjacent to a metro area, 6) urban population of 2,500 to 19,999, adjacent to a metro area, 7) urban population of 2,500 to 19,999, not adjacent to a metro area, 8) completely rural or less than 2,500 urban population , adjacent to a metro area, 9) completely rural or less than 2,500 urban population , not adjacent to a metro area. For clarity, adjacency as defined in this classification describes a non-metro county which physically adjoins one or more metro areas with at least 2% of its employed labor force commuting to central metro cities (48).

Based on scientific evidence, limited access to care for patients living in remote rural areas or in small urban areas far from healthcare services is associated with poorer health outcomes (49, 50). Using 2006-2008 California cancer registry data, Chow et al demonstrated that patient rurality was associated with inadequate lymphadenectomy in patients with stage I to III colon cancer, poor adherence to quality measures and overall, a worse cancer-specific survival. With the growing provision of centralized patient care, rural patients and rural providers may increasingly find quality care a challenge to receive, possibly as a result of the rising financial burden and an increase in travel distance to access this care (51). The RUCC provide more detailed information of residential locality and degree of rurality, and could potentially serve as proxy for analysis of proximity and access to colorectal cancer care.

Rationale and specific aims

In order to better understand the importance of geographic differences and CRC patient care in the United States, this study seeks to investigate the geographic disparity in the survival of colorectal adenocarcinoma following surgery. The study population is limited to early stage, resected CRC in an effort to avoid potential bias from the use of adjuvant chemotherapy which is known to be under ascertained in population-based cancer registry data. We seek to better understand the geographic characteristics related to access to and utilization of colorectal cancer care and determine how these factors are associated with survival. We postulate that survival of colorectal adenocarcinoma following surgery differs by proximity of rural-urban areas to metro areas. Our hypothesis is that non-metropolitan areas further from a metro area are associated with poorer survival outcomes. To test our hypothesis, data from Surveillance, Epidemiology, and End Results (SEER) Program, a US population-based cancer registry system which accounts for approximately 30% of the total US population, will be used (52). SEER collects data on the geographic location of cases using the Rural-Urban Continuum Codes (RUCC). Our analyses focus on adults with a diagnosis of stage 0, I and II invasive colorectal adenocarcinoma made from 2007 to 2011, controlling for sociodemographic and clinical factors such as age, sex, tumor characteristics, race and socioeconomic status. Other factors responsible for the geographic disparity associated with survival outcomes of colorectal adenocarcinoma are also explored.

INTRODUCTION

Colorectal cancer, a leading cause of morbidity and mortality worldwide, is the third most commonly diagnosed cancer and the second leading cause of cancer death among both men and women worldwide (1-4). It comprises about 9.7% of the global cancer burden, with an annual worldwide incidence of approximately 1.3 million cases and a mortality of 700,000 cases (6, 7). In the United States, despite a measurable decline in incidence and mortality over the past two decades, colorectal cancer remains the third most common cancer among men and women combined (4). It is expected that 49,190 deaths from colorectal cancer will occur in the United States in 2016. A decrease in the number of deaths per 100,000 population per year, due in part to enhanced early detection and treatment of colorectal cancer, has increased the 5-year overall survival to about 65%, with variation across socioeconomic status, race and ethnic subgroups (13-15). In general, prognostic factors for CRC survival include tumor stage, grade, histologic type, age at diagnosis, sex, socioeconomic status, race, ethnicity and treatment type. Access to diagnostic and treatment services has also been implicated (16). Although several international and US study findings have shown geographic variation in CRC screening procedures, treatment and survival (25), fewer studies have sought to explore geographic variations in CRC survival using US cancer registry data. Furthermore, very little is known of the variation in CRC survival following colorectal resection; none to our knowledge has done this using US population-based cancer registry data. Based on a study conducted in the Wessex region of southern England, CRC patients living further from a treatment center (more than 30 km) showed worse prognosis following surgery, especially within 30 days of the procedure (44).

For lack of ideal classifications, many research studies in healthcare utilize rural-urban definitions which are based on features such as population density, geographic isolation, population size and socioeconomic deprivation (46, 47). These definitions, albeit indicative of population, education, poverty level and socioeconomic status, may not sufficiently predict access to patient care. The 2013 Rural-Urban Continuum Codes, developed by the United States Department of Agriculture (USDA), form a classification scheme that distinguishes metropolitan (metro) counties by the population size of their metro areas, and non-metropolitan (non-metro) counties by degree of urbanization and adjacency to a metro area (Figure 1) (48). They provide more detailed information of residential locality and degree of rurality, and could potentially serve as proxy for analysis of proximity and access to colorectal cancer care. In order to better understand the importance of geographic differences and CRC patient care in the United States, this study seeks to investigate the geographic disparity in the survival of colorectal adenocarcinoma following surgery. We want to better understand the geographic characteristics related to access to and utilization of colorectal cancer care and determine how these factors are associated with survival. We postulate that survival of colorectal adenocarcinoma following surgery differs by proximity of rural-urban areas to metro areas. Our hypothesis is that non-metropolitan areas further from a metro area are associated with poorer survival outcomes. To test our hypothesis, data from Surveillance, Epidemiology, and End Results (SEER) Program will be used. Our analyses focuses on adults with a diagnosis of stage 0, I and II invasive colorectal adenocarcinoma made from 2007 to 2011, controlling for sociodemographic and clinical factors. Other factors responsible for the geographic disparity associated with survival outcomes of colorectal adenocarcinoma are also explored.

MATERIALS AND METHODS

Data source

Data used for this analysis were obtained from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) which collects cancer incidence and survival data in the United States and constitutes a nationally representative population of U.S. cancer patients. The SEER registry, established in 1973, now represents approximately 30% of the total U.S. population and contains data from 18 population-based cancer registries. These include Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, Alaska Native, Greater California, Kentucky, Louisiana, New Jersey and Greater Georgia. In addition to patient demographics, tumor characteristics and treatment modalities, the SEER Program also collects follow-up data for vital status, largely provided by state vital records and the National Death Index of the National Center for Health Statistics (NCHS) (52). Access to the SEER research data was granted by the NCI and gained using the SEER*Stat statistical software (version 8.2.1). Because this study does not constitute human research, it did not require Institutional Review Board (IRB) approval or review.

Study population

We identified 172,090 cases of colorectal cancer diagnosed between January 1, 2007 and December 31, 2011 from the 18 SEER cancer registries. Using SEER*Stat, we extracted data including male and female cases aged ≥20 years with a diagnosis of colorectal adenocarcinoma (ICD-O-3 C18.0-C18.9, C19.9, C20.9, including histologies 8140-8389 only). We restricted our data to invasive adenocarcinoma with less aggressive histologic types because this cohort was more likely to undergo surgical resection following diagnosis. All unknown and late stage (stages III, IV) colorectal adenocarcinoma cases (n=80,877, 47%) were excluded. Stage 0 was included in the study because based on staging definitions from AJCC it includes cancer cells which have invaded the lamina propria (33). Our choice to select early stage resectable patients for this study was so as to better assess the association between geographic location and our outcome. Because geographic variation in cancer chemotherapy is known to impact cancer survival outcomes (53, 54), and SEER data on chemotherapy is limited, this study focused on early stage colorectal adenocarcinoma with an aim to create a fairly homogenous population of cases that had received local resection or a radical resection. We also excluded from our data patients who had not undergone surgical resection (n=25,422, 14.78%). To further avoid bias, cases which were not microscopically diagnosed (n=570, 0.37%) were excluded from the study.

Because the presence of more than one tumor may affect treatment type and survival outcome, we chose to include cases with a first and only primary tumor. Hence, we excluded patients with more than one primary (n=47,311, 27.49%), non-malignant tumors (n=8159, 4.74%), autopsy only or death certificate records (n=135, 0.08%) and cases in which positive regional lymph nodes were found (n=48,159, 27.98%). Lastly, we excluded cases with no or unknown values for our outcome, survival time (n=7,451, 4.33%). For our survival analysis, we further excluded cases with unknown marital status at diagnosis and race. The final cohort included 50,834 cases.

Study variables

The outcome of interest was survival time, measured in months and defined as the time from cancer diagnosis until death, study endpoint or until censored. The study follow-up endpoint was December 31, 2012. Survival was limited to a maximum of 60 months. The vital status variable classified death from CRC as an event. Our exposure of interest indicating a measure of residential geography at the time of cancer diagnosis was obtained by linking residential county at diagnosis to the 2013 Rural-Urban Continuum codes created by the United States Department of Agriculture (USDA). All US counties were classified into 9 subgroups based on population size, degree of urbanization and adjacency to a metropolitan area (55). For the purpose of this study and in order to address our hypothesis, we reclassified our exposure variable based on proximity to a metropolitan county area into 3 categories: 1) metropolitan area, 2) non-metropolitan area adjacent to a metropolitan county, 3) non-metropolitan area not adjacent to a metropolitan county. The SEER cancer registries were categorized into 4 U.S. regions - Northeast, Midwest, South and West, based on the widely used United States Census Bureau classification (Figure 2).

Major risk factors identified in recent studies to be associated with survival outcomes of colorectal adenocarcinoma were identified as control covariates. These variables of interest identified in SEER included: sex, age at diagnosis, race and ethnicity, marital status at diagnosis, insurance status, poverty level, histologic type, stage and grade at diagnosis, primary cancer site and surgery type. Sex was classified as male and female. Age at diagnosis was categorized as 20-44, 45-59, 60-74 and ≥75 years, race as white, black, other (American Indian, Alaskan Native, Asian/Pacific Islander) and unknown, and ethnicity as Hispanic and Non-Hispanic. Marital status was re-categorized into 3 groups: married;

unmarried, including single (never married), divorced, widowed or separated; and unknown. Socioeconomic status (SES) was assessed using health insurance status - insured, uninsured or any Medicaid and unknown. We also assessed SES using the percentage of persons below the poverty level based on Census American Community Survey (ACS) 2007-2011 classification and categorized this as <10%, 10-19.9% and ≥20%.

Histologic type was classified based on the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) and recoded into 5 categories - adenocarcinoma, not otherwise specified (NOS); adenocarcinoma, adenomatous polyposis coli; papillary adenocarcinoma, NOS and adenocarcinoma, other subtypes. Stage at diagnosis was categorized as 0, I, IIa and IIb based on the derived AJCC Stage Group, 6th edition. Grade at diagnosis was regrouped into low (Grade I, well differentiated and II, moderately differentiated), high (Grade III, poorly differentiated and IV, undifferentiated) and unknown. Primary cancer site was grouped into 4 categories - proximal colon (caecum, appendix, ascending colon, hepatic flexure, transverse colon), distal colon (splenic flexure, descending colon, sigmoid colon), colon NOS (including overlapping lesions of the colon), and rectum (including the rectosigmoid junction). Surgical treatment of the primary site (surgery type) was categorized into limited surgery (local tumor excision, wedge or segmental resection), definitive surgery (subtotal or total colectomy, proctectomy, pull-through surgery with or without ileostomy, colectomy, proctocolectomy with en bloc resection) and surgery NOS.

Statistical analysis

We explored demographic and cancer characteristics with frequency of vital status and geographic location using descriptive and Pearson's chi-square statistics. Bivariate and multivariate analyses were carried out to examine associations between covariates. The proportional hazard assumption was assessed for all variables in our models using a combination of the graphical approach, the log-rank test and the extended Cox model with time-dependent variables. Interaction assessment and collinearity diagnostics between our main exposure variable and covariates were conducted. In order to assess the differences in survival of colorectal adenocarcinoma by geographic location and the SEER regions, adjusted Kaplan-Meier survival curves and multivariate Cox proportional hazard models were constructed. Age at diagnosis, sex, marital status, race, poverty status, stage and grade at diagnosis and surgery type were selected *a priori* and controlled for in our survival analyses. We presented the results of our multivariate analysis as adjusted hazard ratios (HR) with corresponding 95% confidence intervals at a statistical significance level of 0.05. Statistical analyses were conducted using SAS statistical software, version 9.4 (Cary, NC).

The 5-year relative survival of colorectal adenocarcinoma and 95% confidence intervals by geographic location, age at diagnosis, sex, race, marital status at diagnosis, census level poverty, stage and grade at diagnosis and surgery type were calculated using SEER*Stat version 8.3.2.

RESULTS

Demographic and cancer characteristics

Of the 54,482 eligible cases of colorectal adenocarcinoma reported in SEER between 2007 through 2011, 47,639 (87.4%) of cases were located in metro areas, 3,876 (7.1%) in non-metro adjacent to metro areas, and 2,967 (5.5%) in non-metro non-adjacent to metro areas (Table 1a). Fifty-two percent of our study population resided in the Western U.S. region, about 69% were diagnosed at 60 years or older, 52% were male, and 80% were white. A greater proportion of our study population were married (55.3%) and had health insurance (84.8%). Of our entire cohort, approximately 65% of cases had a non-specific adenocarcinoma; 47% and 80% had a stage I and low grade tumor respectively. Approximately 56% of the study participants had received a local tumor excision or a wedge or segmental resection. About 7% of all cases died during the follow-up period (Table 1a). While cases 75 years and older comprised 29% of the population alive at study end, the age group made up 55% of cases that died. We noted that stage I colorectal adenocarcinoma cases made up a majority (48%) of the survivors; on the other hand, mortality was higher in stage IIa cases (52.8%). Overall, we observed significant differences in socio-demographic characteristics when comparing cases from our 3 geographic locations (Table 1b). In the Western region, 94% of cases resided in metro counties, compared to non-metro adjacent (3%) and non-metro non-adjacent (2.8%) areas. An inverse relationship was found to exist between census level poverty and geographic location. Of the patients with a stage I tumor, 88% were located in a metro area, 7% in a non-metro adjacent area and 5% in a non-metro non-adjacent area. High grade colorectal adenocarcinoma at diagnosis was found in 13%, 10% and 11% of patients located in non-metro non-adjacent, non-metro adjacent and metro areas respectively. 27.8% of cases had rectal adenocarcinoma and 72.2% of cases had adenocarcinoma of the colon with a greater proportion originating in the proximal colon. Patients who had received limited surgery were more likely to be located in metro and non-metro non-adjacent areas. Conversely, patients who had received definitive surgery were more likely to be located in non-metro adjacent areas (Table 1b). Cancer characteristics of our study population showed statistically significant differences between geographic locations, except for primary cancer site and surgery type (p-value: 0.1127 and 0.1801 respectively).

Survival analysis

Kaplan-Meier (KM) survival curves comparing geographic location by proximity to a metro area differed significantly (Log-Rank: 8.17, p-value: 0.0168) with survival in non-metro non-adjacent areas slightly less than that in metro areas but greater than that in non-metro adjacent areas (Figure 3). KM curves by US Census region showed better survival in the West compared to other regions (Log-Rank: 22.29, p-value: <.0001) (Figure 4). Table 2 shows 5-year relative survival with corresponding 95% CI of early stage colorectal adenocarcinoma for the cases in the 18 SEER cancer registries diagnosed between 2007 through 2011. Survival estimates were reported for geographic location by proximity to a metro area, age at diagnosis, sex, race, marital status at diagnosis, census level poverty, stage and grade at diagnosis and surgery type. Five-year relative survival was observed to be highest for cases in metro areas (92%) compared to both non-metro areas. Non-metro non-adjacent areas were likewise noted to have better survival estimates compared to non-metro adjacent areas (89.6% vs. 87.3%). Relative survival after 5 years decreased markedly with age, with approximately 88% of cases diagnosed at 75 years or older surviving compared to 93% of cases between 20 and 44 years of age. The 5-year survival was lower among blacks compared to whites (87.3% vs. 92%) and other races (91.7%).

Multivariate analyses of cancer-specific mortality

After excluding cases with unknown marital status at diagnosis and race, a final cohort of 50,834 was analyzed in a multivariate model. The proportional hazard assumptions were satisfied for age at diagnosis, sex, race, marital status, poverty level, stage and grade at diagnosis and surgery type. We found no existing interaction between the exposure of interest and predictor variables. Collinearity assessment indicated no collinearity between the variables in the final model. Table 3 and 4 present results from adjusted multivariate Cox proportional hazard analyses. A statistically insignificant difference in survival was found for cases living in metro and non-metro adjacent areas; a 10% increase in cancer-specific mortality risk was observed among surgically resected early-stage colorectal adenocarcinoma patients in non-metro adjacent areas (p-value: 0.1248). Also, no significant difference in mortality risk was found between metro and non-metro non-adjacent areas (HR: 1.04, 95% CI: 0.90, 1.20). Geographic variability in survival of early-stage colorectal adenocarcinoma was present by US census region. Compared to the Western region of the United States, mortality risk among colorectal adenocarcinoma patients was statistically significantly higher in the South (HR: 1.12, 95% CI: 1.02, 1.22). No significant difference was found to exist between the West and Midwest or Northeast regions. All mortality risk estimates for predictor variables were statistically significant except for age category 45-59 years.

DISCUSSION

Five-year cancer-specific survival analysis of surgically resected early stage colorectal adenocarcinoma suggests that patients residing at the time of diagnosis in metropolitan counties have a higher cancer survival compared to non-metro adjacent areas. This finding was statistically insignificant, however. We also found no statistically significant difference between metro and non-metro non-adjacent areas. Although insignificant, we found it surprising that the unadjusted survival estimates and the adjusted hazard ratio for non-metro non-adjacent areas compared to metro areas was higher than that for non-metro adjacent areas. Based on our hypothesis, we expected that living further from a metro areas would affect access to highly specialized cancer care and survival. Nonetheless, five-year relative survival estimates conducted using the same study population presented a similar pattern of survival. In general, studies have shown that persons living in remote rural areas or in small urban areas located further from metropolitan counties are more likely associated with worse cancer-specific survival (51, 56). The choice to re-categorize our exposure variable as such stems from this precise notion, assuming that proximity from cancer care is associated with cancer survival. To dichotomize the exposure variable into metro and non-metro areas could have masked our study findings. Furthermore, if geographic location were grouped based on population size into metro, urban and rural areas, exploration of the study hypothesis would have been limited since our aim was to determine how proximity to a metro area relates to access to a specialized cancer center.

These unexpected findings of the Cox proportional hazard analysis may suggest that certain preconceived views about metropolitan and non-metropolitan characteristics and cancer survival in the United States are poorly understood. On the other hand, it is entirely possible that our attempt at measuring access to care through the use of county level RUCC codes did not actually capture what was intended. Unfortunately this was the only variable of this type available in the public SEER research data set. Never-the-less, the non-significant but unexpected differences between the non-metro adjacent and non-metro non-adjacent areas are interesting to consider. One of the explanations for these findings could be that access to care is indeed limited in urban areas compared to rural areas. Interestingly, in a 5-year randomized clinical trial (n=126) focused on cancer patients and survivors, American Indians residing in urban areas reported inadequate access to care, public transportation and support as perceived barriers to cancer-related care. On the other hand, rural participants reported communication, language differences and low level of cancer care knowledge as perceive barriers (57). While access to care may prove to be different between non-metro adjacent areas and non-metro non-adjacent areas, cases in more non-metro non-adjacent areas are more likely to have a usual source of care from a regular provider (58).

A second potential explanation of the study results could be immortal time bias. Immortal time is defined as a period of follow-up during which the study outcome cannot be reached until a designated event has occurred (59, 60). In our study, patients who had not undergone surgery would be considered immortal until they did, and patients who did not survive during immortal time could not be included in the study. Inclusion of immortal person-time in the study follow-up period would exceed the actual person-time at risk and bias survival estimates. This study population consisted of patients who had undergone surgical resection. Since this was an inclusion criteria, we may have excluded patients who could not access good surgical care who may have died before a procedure could be performed. In doing this, we thus may have only included ‘healthier’ patients into the study who could have better survival outcomes. If this were done disproportionately between exposure groups, it could affect survival outcomes. Although results of the study were insignificant, we chose to examine the possibility of immortal time bias. We therefore, conducted a similar analysis on a subgroup of the study population including only cases that had received a polypectomy (n=3,695). We chose to analyze this group based on the assumption that these patients, irrespective of geographic location, had received this procedure at the time of colorectal screening at a facility within close proximity to their area of residence and that access to colorectal screening was not different for each location. Under this assumption, immortal time bias would not play a role as we imagine it would in the total study population because the accumulated immortal person-time in this sub-cohort is not in excess of what is expected. Results of this sub-analysis indicated that compared to metro areas, cases in non-metro adjacent areas had a persistently higher risk of mortality (HR: 1.71, 95% CI: 0.89, 3.27) than those living in non-metro non-adjacent areas (HR: 1.13, 95% CI: 0.48, 2.66) after adjusting for all predictors. This pattern also held true for 5-year relative survival estimates between non-metro adjacent, non-metro non-adjacent and metro areas (88.3% vs. 94.1% vs. 94.6%) and suggests that immortal time bias may not entirely be at play in the study analysis.

To further assess the effect of immortal person-time on study results, we explored the survival time of cases who had died between 2007 through 2011 (n=3,718) by geographic location. To do this, the survival time variable was re-categorized into 0-1 months, 2-3 months, 4-5 months and ≥6 months. The proportion of cases who died was found to be higher among cases in non-metro adjacent areas compared to non-metro nonadjacent areas across 3 survival time categories (9.3% vs. 5.5% at 0-1 months, 8.4% vs. 3.3% at 2-3 months, 8.3% vs. 9.5% at 4-5 months and 8.0% vs. 6.0% at ≥6 months). The results of these sub-analyses make an argument against immortal time bias explaining these differences. While it would have been ideal to address this potential bias by initiating survival time from surgery rather than diagnosis, date of surgery was unfortunately not available in the SEER dataset.

Survival analysis of our study population presented some key findings linked with risk predictors. Relative survival estimates suggest that patients with early stage colorectal cancer, when treated with surgery, have better survival outcomes, especially at an earlier age at diagnosis. Compared to cases 20-44 years, adults 75 years and older had lower 5-year relative survival outcomes (88% vs. 93%) with a highly statistically significant adjusted HR of 4.02 (95% CI: 3.27, 4.95). This may either be indicative of the poor attention paid to colorectal cancer screening in this age group or the presence of co-morbid conditions at this age. Future studies may be required to identify the specific underlying factors responsible for these outcomes. Higher survival outcomes were noted for early stage cancer patients who received definitive treatment (HR: 0.90, p-value: 0.0010) compared to a more conservative one. As expected, a higher risk of death was also associated with increasing cancer stage. Compared to stage 0 cancer, stage IIb cancer had a significantly high mortality risk (HR: 11.39, 95% CI: 8.79, 14.76). These and similar results have fueled the need to improve early colorectal cancer screening and detection. Although the association between CRC stage, screening and survival by geographic location is an important relationship to explore, we found this to be beyond the scope of this investigation.

Based on this study population, a larger proportion of blacks reside in metro counties compared to non-metro adjacent and non-metro non-adjacent areas (10.9%, 10.2% and 4.6% respectively). The inverse was found to be the case for white patients (78.5%, 88% and 90.1%). Given that a higher proportion of blacks live in the metro counties compared to the non-metro areas, it might be expected that better outcomes would be found in this racial group. Statistically significant findings of higher mortality risk were, however, found in the multivariate Cox model for blacks compared to whites (HR: 1.28, p-value: <.0001). This indicates the possibility of sociodemographic and economic factors driving this trend. The same may be true for single, separated, divorced or widowed patients compared to married patients (HR: 1.51, p-value: <.0001), where a lack of social support may play a role in influencing cancer survival. Several U.S. based retrospective cohort studies conducted using SEER data have highlighted this impact of social support on cancer detection, treatment and survival (61, 62).

Strengths and Limitations

The relationship between geographic location and colorectal cancer survival has been studied in many countries using statewide and countrywide cancer registries including the SEER database (8, 28, 36, 51). However, no population-based research has been performed in the United States, to the knowledge of the author, to determine differences in early stage surgically treated colorectal cancer survival which may exist as a result of proximity to a metropolitan area, and by inference to cancer care. SEER's 18 cancer registries house data on a significant proportion of the U.S. population and are widely distributed across the country (52). The large sample size of the study population increased statistical power, which lent to the validity of the analyses. In addition, re-categorization of USDA RUCC allowed for our study population to be assessed not only on sociodemographic characteristics, but also by proxy, on proximity from cancer care. The use of the exposure variable in this way provided a more in-depth analysis of the nuances surrounding early stage CRC survival. Furthermore, the use of this data allows for generalizability of study findings and possibly, advances in cancer research and cancer care.

SEER data, however, posed several limitations. While SEER data provides information on major clinical and sociodemographic predictors, data on colorectal cancer screening and time to surgery are not available using SEER public-access database. Lead time is the time added to survival as a result of early screening and diagnosis of cancer. With increasing CRC screening trends, the presence of lead-time bias has become more evident in survival analysis and has been known to exaggerate relative survival estimates; however, because this study mainly focuses on the differences in survival across time, the risk of bias may have been reduced (63). With the ability to identify time to surgery, defined as duration of time from diagnosis to surgery, immortal time bias could have potentially been removed from the study by excluding immortal person-time from the survival analysis (59). Based on the sub-analysis performed earlier, it is anticipated that this bias was insignificant in this study; however, this limitation is worthy of note for future survival studies. More importantly for this study, the lack of facility-related data in SEER created a drawback in the direct assessment of access to and utilization of colorectal cancer care. Provision of variables which describe characteristics of cancer care providers and facilities would diminish the use of proxy variables and improve the accuracy of study findings in future research.

CONCLUSION

Public health implications

The objective of this study was to explore the differences which exist between geographic locations in the United Sates and colorectal cancer survival among individuals who have early stage resectable cancer. The study demonstrated the nuanced relationships existing within metropolitan, non-metropolitan adjacent and non-metropolitan non-adjacent locations as it relates to proximity to cancer care and access to care. Our results did not show that geographic location as it relates to proximity to care and as measured in this study is significantly associated with cancer survival outcome. However, because of the nature of the SEER data and because SEER Program collects county level data or data with some degree of information, this has limited the ability to determine the characteristics impacting individual care. Therefore, there is a strong need for a more robust data source which would provide information such as provider or facility care, distance from cancer facility, chemotherapy treatments and individual data. Attention has been paid to the U.S. Census Bureau’s definitions of geographic locations based on sociodemographic features or population size and density. There is a growing need for variables which take into account geographic characteristics which aid in assessing access to and use of healthcare services among cancer patients, and ultimately, provides value towards improved health outcomes.

Future recommendations

In the bid to further understand the nuances involved in the relationship between geographic location and access to health care as it relates to survival, future population-based studies focused on specific geographic characteristics which impact survival outcomes are recommended.

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TABLES AND FIGURES

Table 1a. Characteristics of a Cohort of U.S. Colorectal Adenocarcinoma Cases in SEER Cancer Registry, 2007-2011[a]

	Vital Status						
	Overall (n=54482)		Alive[b] (n=50560)		Deceased[c] (n=3,922)		p-value[d]
	No.	%	No.	%	No.	%	
Demographic characteristics							
Geographic location							0.0109
Metro	47639	87.44	44267	87.55	3372	85.98	
Non-metro adjacent	3876	7.11	3555	7.03	321	8.18	
Non-metro non-adjacent	2967	5.45	2738	5.42	229	5.84	
US Census regions							<.0001
Northeast	8403	15.42	7746	15.32	657	16.75	
Midwest	5175	9.50	4797	9.49	378	9.64	
South	12762	23.42	11754	23.25	1008	25.70	
West	28142	51.65	26263	51.94	1879	47.91	
Age at diagnosis, years							<.0001
20-44	2620	4.81	2521	4.99	99	2.52	
45-59	14412	26.45	13875	27.44	537	13.69	
60-74	20544	37.71	19403	38.38	1141	29.09	
75+	16906	31.03	14761	29.02	2145	54.69	
Sex							0.0019
Female	26411	48.48	24416	48.29	1995	50.87	
Male	28071	51.52	26144	51.71	1927	49.31	
Race							<.0001
White	43473	79.79	40289	79.69	3184	81.18	
Black	5760	10.57	5280	10.44	480	12.24	
Other[e]	4678	8.59	4427	8.76	251	6.40	
Unknown	571	1.05	564	1.12	7	0.18	
Ethnicity							0.1570
Hispanic	5497	10.09	370	10.41	5127	9.43	
Non-Hispanic	48985	89.91	3552	89.86	45433	90.57	
Marital status							<.0001
Married/living as married	30132	55.31	28469	56.31	1663	42.40	
Single/divorced/widowed/separated	21017	38.58	18958	37.50	2059	52.50	
Not stated/unknown	3333	6.12	3133	6.20	200	5.10	
Census level poverty, % living with poverty							<.0001
<10%	12695	23.30	11876	23.49	819	20.88	
10-19.9%	34613	63.53	32150	63.59	2463	62.80	
≥20%	7174	13.17	6534	12.92	640	16.32	

Table 1a. Characteristics of a Cohort of U.S. Colorectal Adenocarcinoma Cases in SEER Cancer Registry, 2007-2011[a] *(contd.)*

	Vital Status						
	Overall (n=54482)		**Alive[b] (n=50560)**		**Deceased[c] (n=3,922)**		
	No.	**%**	**No.**	**%**	**No.**	**%**	**p-value[d]**
Health Insurance status							<.0001
Insured	46206	84.81	43036	85.12	3170	80.83	
Uninsured/any Medicaid	6639	12.19	5968	11.80	671	17.11	
Insurance status unknown	1637	3.00	1556	3.08	81	2.07	
Cancer characteristics							
Histologic type							<.0001
Adenocarcinoma, NOS	35143	64.50	31974	63.24	3169	80.80	
Adenocarcinoma, adenomatous polyposis coli	7767	14.26	7508	14.85	259	6.60	
Papillary adenocarcinoma, NOS	10981	20.16	10519	20.80	462	11.78	
Adenocarcinoma, other subtypes	591	1.08	559	1.10	32	0.82	
CRC stage[f]							<.0001
0	3735	6.86	3659	7.24	76	1.94	
I	25359	46.55	24391	48.24	968	24.68	
IIa	22128	40.62	20058	39.67	2070	52.78	
IIb	3260	5.98	2452	4.85	808	20.60	
CRC grade							<.0001
Low	43484	79.81	40427	79.96	3057	77.94	
High	5777	10.60	5093	10.07	684	17.44	
Unknown	5221	9.58	5040	9.97	181	4.61	
CRC site							<.0001
Proximal colon	22220	40.78	20503	40.55	1717	43.78	
Distal colon	16492	30.27	15439	30.54	1053	26.85	
Colon NOS	623	1.14	566	1.12	57	1.45	
Rectal	15147	27.80	14052	27.79	1095	27.92	
Surgery type							<.0001
Limited surgery	30881	56.68	28904	57.17	1977	50.41	
Definitive surgery	23429	43.00	21506	42.54	1923	49.03	
Surgery, NOS	172	0.32	150	0.30	22	0.56	

[a]Patients diagnosed with colorectal adenocarcinoma between 2007 and 2011 and followed through 2012 were included in the study.
[b]Includes censored cases.
[c]Death from all causes.
[d]p-values were derived using Pearson's χ^2 test.
[e]American Indian, Asian/Pacific Islander, Native Alaskan.
[f]AJCC staging, 6th Edition.

Table 1b. Characteristics of a Cohort of U.S. Colorectal Adenocarcinoma Cases in SEER Cancer Registry by Geographic Location, 2007-2011[a]

	Geographic Location[b]						
	Metro (n=47639)		Non-Metro Adjacent (n=3876)		Non-Metro Non-adjacent (n=2967)		p-value[c]
	No.	%	No.	%	No.	%	
Demographic characteristics							
US Census regions							<.0001
Northeast	8240	17.30	163	4.21	0	0.00	
Midwest	3833	8.05	685	17.67	657	22.14	
South	9067	19.03	2178	56.19	1517	51.13	
West	26499	55.62	850	21.93	793	26.73	
Age at diagnosis, years							<.0001
20-44	2338	4.91	152	3.92	130	4.38	
45-59	12680	26.62	958	24.72	774	26.09	
60-74	17730	37.22	1594	41.12	1220	41.12	
75+	14891	31.26	1172	30.24	843	28.41	
Sex							0.0005
Female	23245	48.79	1799	46.41	1367	46.07	
Male	24394	51.21	2077	53.59	1600	53.93	
Race							<.0001
White	37389	78.48	3411	88.00	2673	90.09	
Black	5229	10.98	395	10.19	136	4.58	
Other[d]	4483	9.41	49	1.26	146	4.92	
Unknown	538	1.13	21	0.54	12	0.40	
Ethnicity							<.0001
Hispanic	5276	11.07	97	2.5	124	4.18	
Non-Hispanic	42363	88.93	3779	97.5	2843	95.82	
Marital status							<.0001
Married/living as married	26084	54.75	2269	58.54	1779	59.96	
Single/divorced/widowed/separated	18527	38.89	1460	37.67	1030	34.72	
Not stated/unknown	3028	6.36	147	3.79	158	5.33	
Census level poverty, % living with poverty							<.0001
<10%	11963	25.11	491	12.67	241	8.12	
10-19.9%	31428	65.97	1759	45.38	1426	48.06	
≥20%	4248	8.92	1626	41.95	1300	43.82	
Health Insurance status							<.0001
Insured	40520	85.06	3244	83.69	2442	82.31	
Uninsured/any Medicaid	5691	11.95	512	13.21	436	14.69	
Insurance status unknown	1428	3.00	120	3.10	89	3.00	

Table 1b. Characteristics of a Cohort of U.S. Colorectal Adenocarcinoma Cases in SEER Cancer Registry by Geographic Location, 2007-2011[a] *(contd.)*

	Geographic Location[b]						
	Metro (n=47639)		Non-Metro Adjacent (n=3876)		Non-Metro Non-adjacent (n=2967)		p-value[c]
	No.	%	No.	%	No.	%	
Cancer characteristics							
Histologic type							<.0001
Adenocarcinoma, NOS	30578	64.19	2613	67.41	1952	65.79	
Adenocarcinoma, adenomatous polyposis coli	6745	14.16	539	13.91	483	16.28	
Papillary adenocarcinoma, NOS	9787	20.54	690	17.80	504	16.99	
Adenocarcinoma, other subtypes	529	1.11	34	0.88	28	0.94	
CRC stage[e]							0.0040
0	3329	6.99	217	5.60	189	6.37	
I	22207	46.62	1773	45.74	1379	46.48	
IIa	19281	40.47	1649	42.54	1198	40.38	
IIb	2822	5.92	237	6.11	201	6.77	
CRC grade							0.0007
Low	38063	79.90	3115	80.37	2306	77.72	
High	4999	10.49	393	10.14	385	12.98	
Unknown	4577	9.61	368	9.49	276	9.30	
CRC site							0.1127
Proximal colon	19476	40.88	1594	41.12	1150	38.76	
Distal colon	14450	30.33	1128	29.10	914	30.81	
Colon NOS	534	1.12	47	1.21	42	1.42	
Rectal	13179	27.66	1107	28.56	861	29.02	
Surgery type							0.1801
Limited surgery	27079	56.84	2132	55.01	1670	56.29	
Definitive surgery	20412	42.85	1728	44.58	1289	43.44	
Surgery, NOS	148	0.31	16	0.41	8	0.27	

[a]Patients diagnosed with colorectal adenocarcinoma between 2007 and 2011 and followed through 2012 were included in the study.
[b]Geographic location sub-grouped based on adjacency from metropolitan counties.
[c]p-values were derived using Pearson's χ^2 test.
[d]American Indian, Asian/Pacific Islander, Native Alaskan.
[e]AJCC staging, 6th Edition.

Table 2. 5-year Relative Survival of Colorectal Adenocarcinoma among Early Stage[a] Cancer Patients Post-Resection, U.S. SEER Cancer Registry 2007-2011

Variable	**Number of cases (n=50,865)**	**5-year Relative Survival (%)**	**95% CI**
Geographic location			
Metropolitan	44,269	92.0	91.3, 92.6
Non-Metro adjacent	3,712	87.3	84.9, 89.4
Non-Metro Non-adjacent	2,801	89.6	86.8, 91.8
Age at diagnosis, years			
20-44	2,475	92.8	91.0, 94.2
45-59	13,300	93.3	92.5, 94.0
60-74	19,170	92.8	91.9, 93.5
75+	15,920	88.0	86.3, 89.5
Sex			
Male	26,218	91.2	90.4, 92.0
Female	24,647	91.7	90.8, 92.2
Race			
White	41,022	92.0	91.3, 92.6
Black	5,375	87.3	85.3, 89.0
Other[b]	4,468	91.7	89.9, 93.2
Marital status at diagnosis			
Married/living as married	29,935	94.6	93.9, 95.3
Single/divorced/widowed/separated	20,930	86.8	85.7, 87.8
Census level poverty, % living with poverty			
<10%	11,787	93.4	92.1, 94.5
10-19.9%	32,309	92.0	91.3, 92.7
≥20%	6,757	85.4	83.6, 87.1
CRC stage[a] at diagnosis			
0	3,187	98.0	95.9, 99.0
I	23,519	96.1	95.2, 96.8
IIa	21,051	88.4	87.4, 89.4
IIb	3,108	67.6	64.8, 70.2
CRC grade			
Low	40,891	91.8	91.1, 92.4
High	5,464	85.7	83.8, 87.4
Surgery type			
Limited surgery	28,452	91.8	91.1, 92.5
Definitive surgery	22,261	91.0	90.1, 91.1
Surgery, NOS	152	78.2	66.2, 86.4

[a]Actuarial method
[b]AJCC staging, 6th Edition, Stages 0 to II
[c]American Indian, Asian/Pacific Islander, Native Alaskan.

Table 3. 5-Year Multivariate Cox Proportional Hazard Model[a] for the Risk of Colorectal Adenocarcinoma Mortality for Early Stage Cancer Patients Post-Resection by Geographic Location, U.S. SEER Cancer Registry 2007-2011

Variable	Hazard Ratio	95% CI	p-value
Geographic location			
Metropolitan	1.00		
Non-Metro adjacent	1.10	0.97, 1.24	0.1248
Non-Metro Non-adjacent	1.04	0.90, 1.20	0.5996
Age at diagnosis, years			
20-44	1.00		
45-59	1.12	0.90, 1.40	0.2999
60-74	1.72	1.39, 2.12	<.0001
75+	4.02	3.27, 4.95	<.0001
Sex			
Male	1.00		
Female	0.80	0.74, 0.86	<.0001
Race			
White	1.00		
Black	1.28	1.16, 1.42	<.0001
Other[b]	0.85	0.74, 0.97	0.0144
Marital status			
Married/living as married	1.00		
Single/divorced/widowed/separated	1.51	1.41, 1.62	<.0001
Census level poverty, % living with poverty			
<10%	1.00		
10-19.9%	1.10	1.10, 1.20	0.0298
≥20%	1.33	1.18, 1.49	
CRC stage[c] at diagnosis			
0	1.00		
I	1.60	1.24, 2.06	0.0003
IIa	3.71	2.88, 4.77	<.0001
IIb	11.39	8.79, 14.76	<.0001
CRC grade			
Low	1.00		
High	1.28	1.18, 1.40	0.1649
Surgery type			
Limited surgery	1.00		
Definitive surgery	0.90	0.84, 0.96	0.0010
Surgery, NOS	1.83	1.19, 2.82	0.0059

[a]Hazard ratio for cause -specific mortality generated from a Cox Proportional Hazard regression model controlling for age at diagnosis, sex, race, marital status at diagnosis, county level poverty status, stage at diagnosis, grade at diagnosis and surgery type.

[b]American Indian, Asian/Pacific Islander, Native Alaskan.

[c]AJCC staging, 6th Edition

Table 4. 5-Year Multivariate Cox Proportional Hazard Model[a] for the Risk of Colorectal Adenocarcinoma Mortality for Early Stage Cancer Patients Post-Resection by U.S. Census Region[b] , U.S. SEER Cancer Registry 2007-2011

Variable	Hazard Ratio	95% CI	p-value
US Census region			
West	1.00		
Northeast	1.10	0.99, 1.21	0.0748
Midwest	1.02	0.90, 1.14	0.8010
South	1.12	1.02, 1.22	0.0129
Age at diagnosis, years			
20-44	1.00		
45-59	1.13	0.90, 1.40	0.2939
60-74	1.72	1.39, 2.13	<.0001
75+	4.03	3.27, 4.96	<.0001
Sex			
Male	1.00		
Female	0.80	0.75, 0.86	<.0001
Race			
White	1.00		
Black	1.25	1.12, 1.38	<.0001
Other[c]	0.87	0.76, 0.99	0.0441
Marital status			
Married/living as married	1.00		
Single/divorced/widowed/separated	1.51	1.41, 1.62	<.0001
Census level poverty, % living with poverty			
<10%	1.00		
10-19.9%	1.12	1.02, 1.22	0.0141
≥20%	1.34	1.19, 1.51	<.0001
CRC stage[d]			
0	1.00		
I	1.60	1.24, 2.06	0.0003
IIa	3.70	2.88, 4.77	<.0001
IIb	11.40	8.79, 14.77	<.0001
CRC grade			
Low	1.00		
High	1.29	1.18, 1.40	<.0001
Surgery type			
Limited surgery	1.00		
Definitive surgery	0.89	0.84, 0.95	0.0008
Surgery, NOS	1.78	1.15, 2.73	0.0091

[a]Hazard ratio for cause -specific mortality generated from a Cox Proportional Hazard regression model controlling for age at diagnosis, sex, race, marital status at diagnosis, county level poverty status, stage at diagnosis, grade at diagnosis and surgery type.
[b]SEER cancer registries categorized by U.S. Census region; source: U.S. Census Bureau
[c]American Indian, Asian/Pacific Islander, Native Alaskan.
[d]AJCC staging, 6th Edition

Figure 1. 2013 Rural-Urban Continuum Codes depicting Metro and Non-Metro counties in the United States, United States Department of Agriculture (USDA)

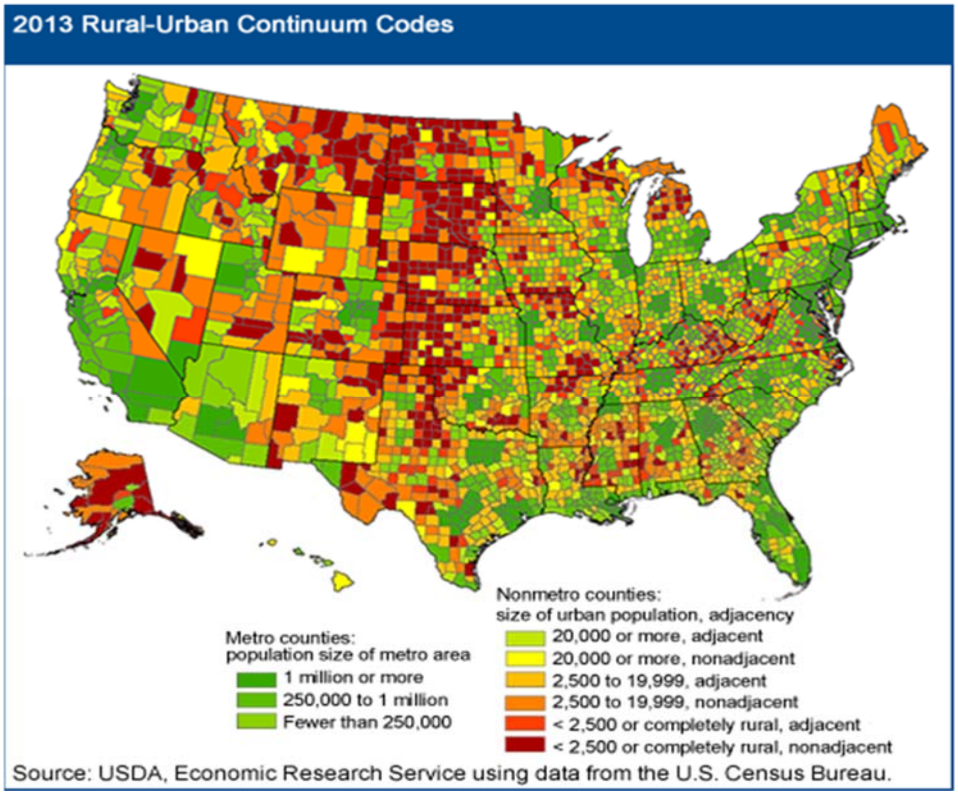

Figure 2. U.S. Census Regions and Divisions, U.S. Census Bureau

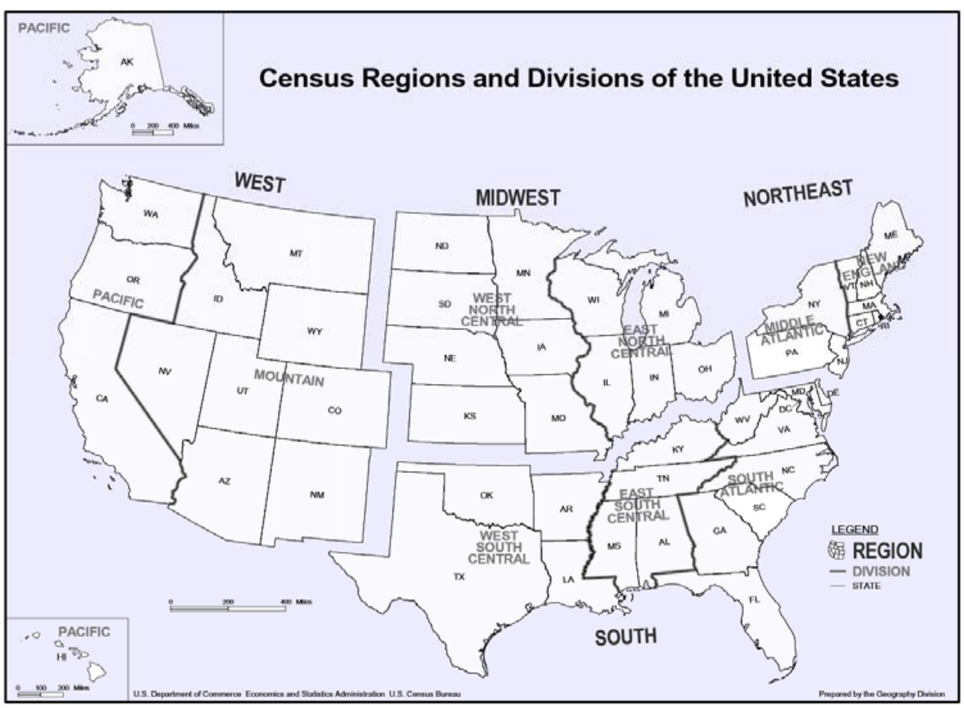

Figure 3. Kaplan-Meier Survival Curves by Geographic Location, U.S. SEER Cancer Registry 2007-2011

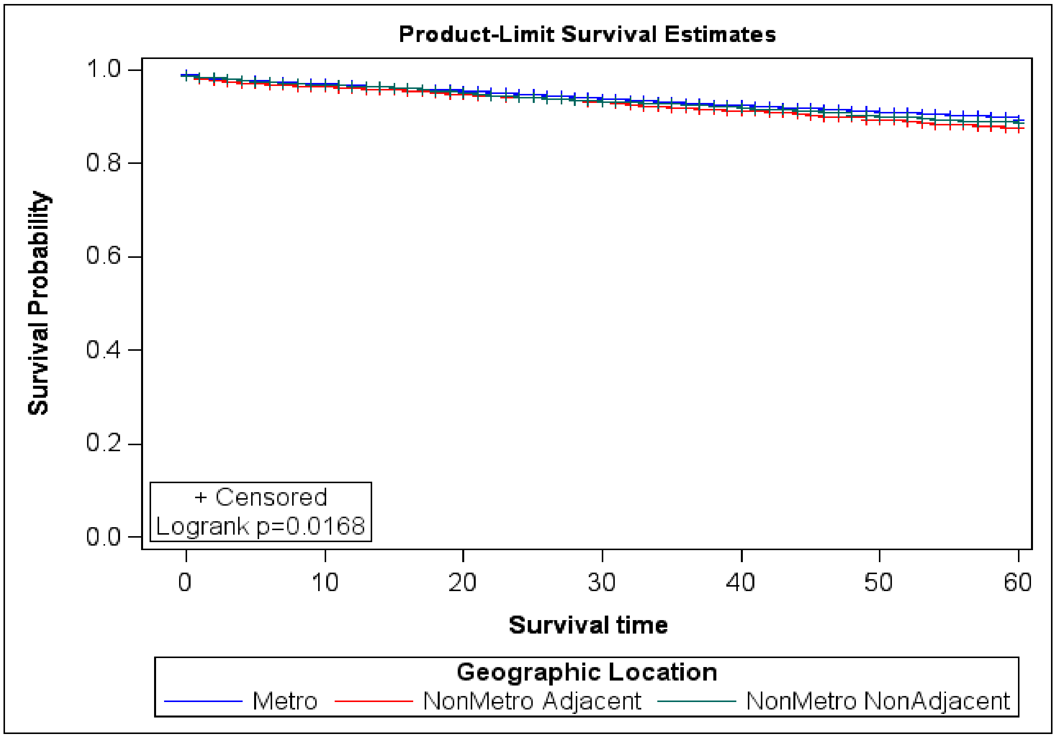

Figure 4. Kaplan-Meier Survival Curves by U.S. Census region, U.S. SEER Cancer Registry 2007-2011